Improvement in Selection of Study Participants

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Introduction.

The screening and pre-selection of suitable subjects for inclusion in clinical trials have long been an accepted practice in the medical field. In order to separate those subjects who will discriminate best between test and control agents, it is recommended that both those likely to develop little or no disease and those likely to be overwhelmed by the disease process be excluded from a trial. By eliminating these subjects, a diminution of the therapeutic or preventive effect will be avoided, and a clearer picture of the agent's biological activity will be obtained.

In order to understand the role of pre-selection in the field of clinical testing of caries prophylactic agents, it is necessary to appreciate first that there are two fundamentally different types of clinical trial, each with its own distinct set of aims and underlying statistical theory. The distinction was drawn some 15 years ago in the general medical field by Schwartz and Lellouch[1], who used the terms "explanatory" and "pragmatic" clinical trial. This refinement was first recognized in dental epidemiology by O'Mullane[2], who considered that the clinical testing of an agent should be conducted as a two-stage process. The first stage was defined as an experimental clinical trial, and the second as a community clinical trial.

The experimental (or explanatory) clinical trial is designed to test the effectiveness of a new agent following encouraging results from initial laboratory work. The agent is tested under ideal conditions contrived in order to allow it every chance to demonstrate its biological effect in preventing or treating the disease. By definition, the sample of subjects involved is drawn from an infinite, hypothetical population of samples similar to the one under study, and the underlying statistical methods are those of hypothesis-testing and estimation theory. The aim is to identify useful agents and establish their efficacy as quickly as possible.

The community (or pragmatic) clinical trial, on the other hand, is designed to evaluate the efficiency of those agents of proven effectiveness which are to become part of public health programs. The agent is therefore tested under real-life conditions employing a sample of subjects with characteristics fully representative of the population on which it will eventually be used. Acceptance procedures known as Decision Theory are involved, and the inferences drawn relate to a real population. The aim is to decide on which therapy to promote, taking into account factors such as cost and acceptability.

A failure to appreciate this distinction in methodology, and an attempt to combine both types of procedure in one and the same trial, led to a confusion of aims in many trials in the past, with a consequent impairment of their efficiency. Thus, samples included many unsuitable subjects, thereby lacking homogeneity, and were consequently often unnecessarily large for the purposes of establishing efficacy. Yet the trial conditions remained so artificial as to give a false and misleading impression of the cost-effectiveness of the agent and its value under real-life conditions. The investigators failed to recognize that if the efficacy of an agent is unknown, assessing its value as a public health measure is irrelevant.

Because the experimental clinical trial is conducted under conditions designed to give the agent the best chance of demonstrating its effect, pre-selection of subjects is an essential technique to adopt in order to improve its efficiency.

Reasons for pre-selection.

Experimental clinical trials of caries prophylactic agents are inevitably expensive and long-term, and it has always been important to ensure that they are conducted as efficiently as possible so that the cost and time period needed to develop a new agent are reduced to a minimum. However, two recent developments have accentuated the need to obtain optimum efficiency in trial design: first, the introduction of standard active control agents, and, second, the general decline in caries prevalence.

Under these changed conditions, caries prophylactic trials in the future will be conducted increasingly to test for small improvements in efficacy of new agents compared with a standard control, or, alternatively, to establish similarity in their biological activity. If traditional experimental designs were followed[3], unacceptably large sample sizes would be required in order to detect these small differences.

Basis for pre-selection.

Variables that can be used as a basis for pre-selection fall into two categories. The first are those that can be documented without examining the subjects, such as age, sex, and social class, while the second group are those that can be recognized only by clinical examination, such as previous caries experience and tooth surfaces at risk. The first group may be conveniently termed "pre-clinical examination criteria" and the second group "post-clinical examination criteria." The use of the second group of variables suffers the disadvantage that a larger sample of volunteers must be screened than may be required for inclusion in the trial, and those who do not meet the selection criteria are rejected.

Pre-clinical examination criteria. – The most consistent criterion for selection in caries clinical trials in the United Kingdom has been age. Subjects aged initially 11 to 12 years have usually been chosen because they are entering a period of high caries activity, as many permanent teeth erupt, and are also likely to remain at the same school throughout the trial period.[4] Age is a sensitive factor, and even one year's difference in the age at which children are admitted to a clinical trial may be important. This can be demonstrated by comparing the t values for differences in mean caries increment between test and control groups over two successive years of a clinical trial (Table 1). Thus, a study employing children initially aged 11 to 12 years may be less efficient than one that begins with children a year older. The advantage of involving older children is that more permanent teeth have erupted, and a greater discrimination between test and control groups may be observed at

TABLE 1
MEAN DFS INCREMENTS IN CHILDREN AGED INITIALLY 11 TO 12 YEARS IN A TEST AND PLACEBO CONTROL GROUP DURING THE FIRST AND SECOND YEAR OF A FLUORIDE DENTIFRICE TRIAL[15]

	First-year DFS Increment	Second-year DFS Increment
Control	2.4	3.5
Test	2.4	2.8
Diff.	0.0	0.7
t Value	0.1	2.1

TABLE 2
32-MONTH MEAN DFS INCREMENTS IN BOYS AND GIRLS IN AN ACTIVE CONTROL FLUORIDE DENTIFRICE TRIAL[12]

	Mean DFS			
	Active Control	Test	Diff.	*t* Value
Boys	3.7	4.6	0.9	1.6
Girls	3.5	4.1	0.5	1.3

TABLE 3
BASELINE DMFT AND PERCENTAGE OF SUBJECTS WITH ZERO INCREMENT IN ACTIVE CONTROL GROUPS IN FIVE CARIES PROPHYLACTIC CLINICAL TRIALS[8-10,12,15] COMMENCING OVER A TEN-YEAR PERIOD

Trial	Baseline year	Baseline Mean DMFT	% of Subjects with Zero Increment
A[10]	1968	5.6	3
B[8]	1970	5.4	14
C[9]	1972	4.5	15
D[15]	1975	4.3	16
E[12]	1977	3.8	24

TABLE 4
MEAN DIFFERENCES IN DFS INCREMENT AND REQUIRED SAMPLE SIZES FOR SUBJECTS IN DIFFERENT CATEGORIES OF INITIAL DMFS EXPERIENCE IN THREE FLUORIDE DENTIFRICE TRIALS[8,12,15]

	Trial B[8] 1970 Placebo		Trial D[15] 1975 Placebo		Trial E[12] 1977 Active	
IDMFS	Diff.	N	Diff.	N	Diff.	N
Low	2.3	22	1.5	65	0.2	2000
Middle	2.8	25	2.0	30	0.6	273
High	2.0	81	2.5	41	2.1	53

an earlier stage in the trial, thus providing the opportunity of conducting clinical trials over a shorter period.

Confining the study population to a particular sex, depending on the type of agent, has been considered[5], following the observation that girls demonstrated a larger treatment response in fluoride dentifrice trials than did boys[4,6-9], although boys proved more discriminating when the agent was in the form of a mouthrinse[10,11]. The main reason for girls benefiting more than boys in placebo-controlled dentifrice trials was probably their more conscientious use of the product. However, the advent of the standard active control has removed sex difference in treatment response as a useful basis for pre-selection. This is illustrated by a recent study carried out in the northwest of England[12], where a low-concentration fluoride dentifrice was compared with a higher fluoride active control (Table 2). There was a larger mean difference of 0.9 DFS for boys than that of 0.5 for girls and, since the numbers of boys and girls were similar, the *t* values may be compared. It can be seen that the *t* value of 1.6 for boys was larger than that of 1.3 for girls. The findings of this study may not be so much at variance with the results of earlier studies as first appears, since an examination of the mean DFS increments shows that the girls benefited more from the lower fluoride dentifrice than did the boys. A similar finding of boys' apparent enhanced discriminatory ability has been reported by other workers conducting a trial employing an active control.[13]

Post-clinical examination criteria. — The most useful variable for pre-selection obtainable by clinical examination is past caries experience. The increment of new caries occurring during the course of a clinical trial is correlated with the caries experience of the subjects at baseline[14], and it is the difference in mean increment between the test and control groups and its variability that determines the magnitude and significance of the treatment effect. However, the progressive decline in caries prevalence and the introduction of active control agents have altered the way in which initial caries experience may be used advantageously in pre-selection.

Table 3 presents the mean DMFT at baseline and the percentage of subjects with zero increment over three years for the active groups of five clinical trials carried out in the northwest of England[8-10,12,15] on children who were aged initially 11 to 12 years. It is apparent that as caries prevalence fell from 5.6 DMFT in 1968 to 3.8 DMFT in 1977, the percentage of subjects with zero increment increased from 3 to 24%.

Subjects who experience very small increments over the trial period are generally not useful in discriminating between the relative efficacy of treatments. This can be demonstrated with data from three clinical trials that commenced in 1970[8], 1975[15], and 1977[12] (Table 4). For the purposes of analysis, the subjects were divided at the 33rd and 66th percentiles, after examination of the frequency distributions of their baseline caries experience, into low, middle, and high initial caries experience groups. The difference between the three-year mean DFS increments for the test and control groups is shown for each trial. Also shown is the minimum sample size *per* group required in order to obtain statistical significance at the 5% level, assuming that a selected sub-group based on each of the three bands of initial caries experience had been used.

It is evident that the pre-selection of subjects in the low and middle bands of initial DMFS would have produced some improvement in efficiency in the 1970 trial from a reduction in the required sample size, and pre-selection of those in the middle band some improvement in the 1975 trial. However, in the active control trial, which commenced in 1977, it is the high initial caries group that would have produced the most efficient trial. It is also noteworthy that the improvement in efficiency that would have resulted from using pre-selection is of a far higher order in this than in the earlier trials.

The number of sound surfaces at risk to caries has also been investigated as a basis for pre-selection, since this too is related to future caries activity — hence the treatment response to preventive agents. In a retrospective analysis of two placebo-controlled trials[5], the value of initial surfaces at risk was enhanced when the presence of only

TABLE 5
MINIMUM SAMPLE SIZES REQUIRED IN FOUR FLUORIDE DENTIFRICE TRIALS[8,9,12,15] WITH AND WITHOUT EXCLUSION OF SUBJECTS WITH DMFS(e) <3

Trial	Unselected	DMFS (e) <3 Excluded
B[8]	42	28
C[9]	67	26
D[15]	55	42
E[12]	317	72

TABLE 6
SENSITIVITY AND SPECIFICITY OF DMFS(e) <3 AS A PRE-SELECTION CRITERION FOR IDENTIFYING SUBJECTS IN THE ACTIVE CONTROL GROUP OF A FLUORIDE DENTIFRICE TRIAL[12] WHO HAD ZERO INCREMENT

Sensitivity	=	0.46
Specificity	=	0.75

certain key surfaces, either sound or unerupted, was used as the pre-selection criterion. In this study, by including the requirement that subjects should have at least half their pre-molar and second molar teeth at risk, in addition to their falling within a specified range of initial DMFS, it was shown that further gains in efficiency could be achieved over and above those resulting from pre-selection on IDMFS alone as a post-clinical examination criterion. However, more recent work has shown that the particular set of surfaces that will provide the best result in a trial appears to some extent data-base-dependent, so that the method lacks the robustness necessary for practical use.

The current status of pre-selection.

In the clinical field, screening procedures are used to identify high risk patients in need of diagnostic investigation and probable treatment. The use of screening to select subjects likely to discriminate best between test and control agents in a clinical trial is not necessarily synonymous, for those most at risk may overwhelm the effect of the test agent. It appears, however, that in caries prophylactic clinical trials, the use of active controls coupled with the general decline in caries has meant that those at high risk to the disease are becoming increasingly the same group which will best discriminate in the trial. This is because the large numbers of subjects whose attack by caries was so severe that they remained largely defenseless, despite the prophylactic agent, can no longer be expected. Since the so-called high band of initial caries experience is disappearing, selection techniques should now be centered on eliminating subjects who are sufficiently caries-resistant that they can be expected to contribute virtually nothing to the detection of treatment differences within a reasonable time span. Thus, all the risk subjects are now those who tend to discriminate between treatment groups.

Of the first group of variables, it is apparent that age has become the most important pre-clinical examination criterion, and that careful consideration should be given to selecting subjects of the optimum age for discriminating between treatments. Of the post-clinical examination criteria, initial DMFS is currently the most useful variable for selecting out those low-risk subjects who are unlikely to contribute to the detection of treatment differences. However, the unmodified IDMFS score is a very crude indicator for selecting discriminating subjects.

Recent research has concentrated on refining and improving the initial DMFS variable as a basis for selection. To this end, a modified DMFS index was investigated in which the caries experience on occlusal surfaces of permanent first molars was excluded. The rationale for this was that the majority of caries attack occurs on these surfaces before the age of nine, so that the past caries experience exhibited is of doubtful relevance in predicting risk levels in young adolescents. In addition to this, permanent first molars extracted were excluded, since the reason for extraction is generally unknown. This modified index was designated DMFS (e), the (e) standing for exclusion.

Table 5 indicates the minimum sample sizes *per* group that would have been required in four clinical trials[8,9,12,15] in order to demonstrate a statistically significant difference between test and control agents at the 5% level. The first column shows the number of subjects required with no pre-selection, while the second column shows the minimum number required after exclusion of those subjects with DMFS (e) <3. It is evident that, in all four trials, the sample size required after excluding subjects with low initial DMFS (e) scores was considerably smaller than that required with the unselected sample. Moreover, the DMFS (e) index was found to have two important advantages over the unmodified DMFS index. First, a group selected on the basis of DMFS (e) was capable of greater discrimination than any group selected on unmodified DMFS. Secondly, selection on the modified index was reliable in both placebo and active control trials, indicating its robustness as a criterion. However, there is room for further improvement in this screening index. When the sensitivity and specificity of DMFS (e) <3 was examined for its ability to screen out subjects in the active control group, which had zero increment, the index was found to be relatively insensitive. It is apparent that, on the basis of probability, only 46 out of every 100 subjects with subsequent zero increment would be excluded (Table 6).

Conclusions.

This overview of the use of pre-selection of subjects in experimental clinical trials of caries prophylactic agents has indicated that the main thrust for future research should be toward refining criteria that will enable those who are likely to experience little or no caries over the course of a trial to be correctly identified. It is through the exclusion of this group of subjects that the greatest gains in efficiency are likely to be achieved in future trials.

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Improvement in Selection of Study Participants: Discussion of Dr. Downer's Presentation

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Introduction.

The reduction in caries experience in the developed countries and the introduction of standard active controls have highlighted our need to increase the efficiency of caries prophylactic trials. The comparison of a standard active control with a new formulation, although not new in medical research, is a relatively new approach in caries prophylactic trials.

Downer and Mitropoulos have proposed that we follow the example of medical researchers and refine the nature of the test hypothesis with the expectation of gains in the efficiency of the trial. They base their assumption on the work of Schwartz *et al.*[1], who partitioned trials into explanatory and pragmatic trials. The adoption of this explanatory approach would enable research workers to perform more efficient trials, although with some lack of generality of application. This change in clinical trial design is long overdue.

Pre-clinical examination selection.

On the basis of a literature survey and analysis of additional data sets[2-4], it is possible to confirm most of the conclusions of Downer and Mitropoulos regarding preselection by age and sex. Age and, by implication, dental age are probably the most important factors in the selection of subjects. Lind *et al.*[5] showed that, when an identical caries prophylactic agent was tested in two different age groups – namely, 8- and 11-year-old subjects – a significant result was achieved one year earlier with the older age group.

Prior to the advent of standard active controls, it was possible to argue that the selection of girls would provide a more efficient experiment when dentifrices were tested, while boys would provide a more efficient test of a mouthrinse or professional applications of APF gel[2,6]. However, some recent trials indicate that there is no advantage in single-sex studies.[4,7]

Post-clinical examination selection.

Downer has been the leading advocate of post-clinical examination selection to reduce group sizes in caries prophylactic trials. In Copenhagen[6], he proposed that the selection of subjects with six specific key surfaces at risk would improve clinical trial efficiency. Independent statistical analysis of other data sets in the U.K.[8] and Boston[9] have failed to confirm the effectiveness of these pre-selection criteria, and in their current report the authors now acknowledge that pre-selection of specific key surfaces is data-set-dependent.

Prior to discussing the new selection criteria of Downer and Mitropoulos, we ought to remind ourselves of the formula that governs sample size. Schwartz *et al.*[1] have shown that the minimum number of subjects needed in each group is:

$$n = (\epsilon_\alpha + \epsilon_\beta)^2 \cdot \frac{2\sigma^2}{\Delta^2}$$

where:

(a) ϵ_α and ϵ_β corresponded to the error rates α and β, respectively;
(b) σ^2 is the variance of the variable under study (it is assumed that the variance is the same for both groups); and
(c) Δ (delta) is the difference between the true group means.

The authors have already established that the delta component is being eroded by the use of standard active controls and the decline in prevalence. However, recent data from the southeast of England[10] have shown that,